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IGF-1: Elixir for Motor Neuron Diseases

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Modulation of testosterone levels is a therapeutic approach for spinal and bulbar muscular atrophy (SBMA), a polyglutamine disorder that affects the motor neurons. The article by Palazzolo et al. in this issue of *Neuron* provides compelling evidence that the expression of insulin growth hormone is a potential therapeutic for SBMA.

Spinal and bulbar muscular atrophy (SBMA), a rare neurodegenerative condition (Fischbeck, 1997), was first described by William R. Kennedy in 1968 (Kennedy et al., 1968), who recalled the first case as being "an exciting patient." Since this first report, it took about two decades to locate the genetic marker on the proximal long arm of the X chromosome (Fischbeck et al., 1986) and identify the presence of CAG expansion within the first exon of the androgen receptor (AR) gene in SBMA (La Spada et al., 1991). This cardinal genetic defect first discovered for SBMA classifies it into the group of polyglutamine (polyQ) neurodegenerative disorders with the classical phenotypic features including anticipation of disease onset associated with a threshold of expanded CAG repeats, cytoplasmic/nuclear inclusions, and mitochondrial dysfunction. The unique character of the individual proteins affected by the polyglutamine expansion reflects distinct pathologies and symptoms for these diseases. The pathophysiology for SBMA consists of fasciculations, proximal muscle weakness, and sensory atrophy without affecting cognitive function, unlike Huntington's disease and spinocerebellar ataxias (Kennedy et al., 1968; Sobue et al., 1989; Sperfeld et al., 2002). Although SBMA progresses rather slowly, the prognosis is poor due to complications associated with respiratory infection (Sobue, 2003). To date, available treatments limit testosterone levels to prevent translocation of the mutant AR to the nucleus and aggregate formation. This approach might partially prolong the lifespan of patients and ameliorate some of the debilitating symptoms of the condition. However, side effects associated with infertility, gynecomastia, and the inability of some androgen antagonists (e.g., flutamide) to effectively reverse SBMA phenotype limit treatment options for this disorder.

What is our current understanding of how mutant AR causes neurodegeneration? Many questions remain unanswered for the myriad nuclear and cellular abnormalities caused by polyQ diseases, but AR has a known function as a steroid hormone receptor and this has significantly advanced our understanding of the mechanism of neurodegeneration causing this disease. In the SBMA field, the ligand-dependant hypothesis is prevalent to model SBMA pathology. Upon ligand binding, the AR, which contains a nuclear localization signal, undergoes a series of conformational changes and translocates to the nucleus by means of heat shock protein 90. Nuclear localization of mutant AR in the presence of androgens is required for SBMA (Katsuno et al., 2002; Montie et al., 2009). Transcriptional deregulation (e.g., inhibition of cellular proteins including CBP protein) and dysfunctional protein processing are primarily responsible for formation of nuclear inclusions (Ellerby et al., 1999; McCampbell et al., 2000; Sopher et al., 2004).

In this issue of *Neuron,* Palazzolo et al. (2009) refine the ligand-dependent hypothesis and provide a novel way to correct aberrant signaling mediated by mutant AR using insulin-like growth factor-1 (IGF-1). IGF-1 is a widespread classical hormone involved in cell growth and in some cases brain plasticity. With a series of elegant in vitro assays using COS1 cells transfected with human mutant AR65, the authors demonstrate that phosphorylation of Akt at serine 473 is stimulated by the addition of IGF-1. The activation of Akt decreases AR-mediated aggregation by 68%. AR aggregation was dependent on activation of the PI3K/Akt pathway and phosphorylation of AR by Akt since PI3K inhibitor LY294002 blocked IGF-1-mediated reduction in aggregation.

From these data, Palazzolo et al. (2009) hypothesize that one of the mechanisms in which IGF-1 exerts its beneficial effect is through phosphorylation of Akt at serine 473 residue, and subsequently, AR at serine 215 by Akt selectively in SBMA muscle. To evaluate the potential benefit of exogenous IGF-1 in vivo, SBMA mice overexpressing human AR97Q were crossed with mice that overexpress a muscle-specific isoform of IGF-1 selectively in skeletal muscle. Akt was activated and phosphorylation of AR at serine 215 occurs in these mice. Furthermore, IGF-1 rescues behavioral and histopathological abnormalities, delays disease onset, and prolongs the lifespan of SBMA mice. IGF-1 also attenuates the morphological and molecular signs of myopathic and neurogenic muscle pathology and increases motor neuron survival.

Based on a series of gain- and loss-of-function experiments, Palazzolo et al. (2009) clearly demonstrate that IGF-1 promotes clearance of mutant AR through the ubiquitin-proteasome pathway in a phosphorylation-dependant manner. Using a cotransfection method in HEK293T cells with constructs expressing HA-ubiquitin mutated AR and phospho-defective AR construct, they reported reduced ubiquitilation of the phosphor-defective AR. Subsequent experiments utilizing the proteosome inhibitor MG132 indicate a dose-dependent inhibition of the IGF-1-mediated clearance of AR. Supply of rapamycin did not influence

AR clearance, excluding autophagy as a mechanism of IGF-1 action. The present study highlights the importance of post-translational modifications of proteins harboring CAG repeats in reversing adverse neurodegenerative effects of polyQ disorders.

It has been shown previously that altering testosterone levels by castration of males (Katsuno et al., 2002) or supply of leuprorelin (Katsuno et al., 2003), a luteinizing hormone releasing hormone (LHRH) analog, which inhibits production of testosterone by the testis, relieved adverse symptoms associated with SBMA in a mouse model, including nuclear localization of AR and formation of inclusions. Similarly, Takeyama et al. (2002) reported that supply of androgen accelerated neuronal degeneration, nuclear inclusions, and conformational alterations of the AR in a fruit fly model overexpressing mutated hAR. Without underestimating the importance of those studies, the approaches described here promote the clearance of the mutant AR and offer an alternative therapeutic strategy for SBMA.

IGF-1 has other therapeutic mechanisms in addition to those proposed by Palazzolo et al. (2009). In a related study on amyotrophic lateral sclerosis (ALS), IGF-1, delivered with adeno-associated virus to the muscle, was shown to prolong the lifespan and delay disease progression in mouse models of ALS (Kaspar et al., 2003). ALS is distinct from SBMA in the rapid progression of the disease. However, both are lethal neuromuscular diseases leading to atrophy of limb and respiratory muscles and loss of motor neurons. These studies were reported seven years ago and therefore progress to validate this therapeutic treatment in ALS has moved slowly. Further, the influence of IGF-1 on the levels of vascular endothelial growth factor (VEGF) has not been considered. VEGF has been shown to be essential for motor neuron survival and plays an important role in SBMA (Sopher et al., 2004). IGF-I is an effective inducer of VEGF secretion and mRNA expression in some cell types (Kaczmarek et al., 2008).

In summary, Palazzolo et al. provide compelling evidence that IGF-1 treatment results in a dramatic extension of lifespan and functional recovery of SBMA mice. Further studies directed at developing a therapy for SBMA patients with IGF-1 or compounds with similar mechanism of action are warranted. Clearly, in light of this work and prior studies, the mechanism by which IGF-1 blocks muscle atrophy should be explored as this may be relevant to other diseases. Finally, IGF-1 promoted clearance of mutant AR and this approach may be relevant to a number of diseases caused by protein misfolding.

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